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Review

Neurobiological origin of psychogenic nonepileptic seizures: A review of imaging studies

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ABSTRACT

Psychogenic nonepileptic seizures (PNES) are relatively common occurrences in epilepsy centers. Pathophysiology of PNES is still poorly understood. In this paper, the evidence for a neurobiological origin of PNES will be reviewed. Recent evidence suggests altered functional and structural brain connectivity as an underlying pathophysiological mechanism in patients with PNES. Pursuing the concept of connectome in patients with PNES and comparing the findings with healthy individuals may result in a breakthrough in identifying the exact neurobiological origin of PNES. Finding the neurobiological bases and identification of biomarkers of PNES will potentially have important clinical implications in formulating better diagnostic and therapeutic approaches for affected patients.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are relatively common occurrences in epilepsy centers [1,2]. The International League Against Epilepsy (ILAE) has identified PNES as one of the 10 key neuropsychiatric issues associated with epilepsy [3]. These seizures consist of paroxysmal changes in responsiveness, movements, or behavior that resemble epileptic seizures but lack a neurobiological origin similar to epileptic seizures and are not associated with electrophysiological epileptic changes [4–6]. The mere explanation that PNES are not epileptic phenomena is not satisfactory. The labels affixed to such patients reflect the prevailing etiological assumptions of their times; hysterical seizures, conversion seizures, functional seizures, pseudoseizures, psychogenic seizures, nonepileptic attack disorder, and finally, psychogenic nonepileptic seizures (PNES) are some of the terms that have been used to describe this disorder. The pathophysiology of PNES is still poorly understood. Psychogenic nonepileptic seizures occur in a heterogeneous patient population. No single mechanism or underlying etiology has been identified that is necessary and sufficient to explain PNES in all patients [6–8]. However, disturbances of the autonomic nervous system have been reported in patients with PNES [9]. In addition, clinical experience suggests that PNES commonly start in association with or during a period of exacerbation of another mental disorder. A lifetime history of other somatoform or dissociative disorders is found in more than 50% of patients who have PNES. Anxiety or psychotic and bipolar disorders are also found more frequently in patients who have PNES than in the general population. Many patients with PNES have features of posttraumatic stress disorder [7]. Finally, there is recent evidence, including findings based on advanced EEG and imaging techniques, which point to specific neurobiological dysfunctions in these patients [10].

Finding the neurobiological bases and identification of biomarkers of PNES will potentially have important clinical implications in formulating better diagnostic and therapeutic approaches for affected patients. In this paper, the evidence from imaging studies for the neurobiological origin of PNES will be reviewed.

2. Methods

The electronic database PubMed was searched on July 1st, 2015 using the following search terms in the English language in the Title/Abstract: “pseudoseizures” OR “nonepileptic attack disorder” OR “psychogenic nonepileptic seizures” OR “nonepileptic seizures” OR “psychogenic seizures” AND “imaging” OR “functional imaging” OR “MRI” OR “fMRI” OR “connectivity”. In the context of this review, PNES were defined as above (see the Introduction), and relevant original studies were included only if it was clear that the phenomenon being referred to was PNES. In total, 15 original studies met the criteria for inclusion (Table 1).

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Table 1
The original imaging studies investigating the neurobiological origin of psychogenic nonepileptic seizures.

Paper	Type of study	Number of subjects with PNES	Healthy control	Clinical recruitment	Psychiatric assessment
Reuber et al. (2002)	Traditional MRI	206	No	Video-EEG recording	Yes (in some)
Jones et al. (2010)	Traditional MRI	221	No	Video-EEG recording	Yes
Devinsky et al. (2001)	Traditional MRI	311	No	Video-EEG recording	Yes
Labate et al. (2012)	Advanced MRI	20	Yes	Video-EEG recording	Yes
Ristić et al. (2015)	Advanced MRI	37	Yes	Video-EEG recording	Yes
Hernando et al. (2015)	Advanced MRI	8	Yes	Video-EEG recording	Not clearly mentioned
Lee et al. (2015)	Advanced MRI	16	Yes	Video-EEG recording	Yes
Ding et al. (2013)	fMRI	20	Yes	Video-EEG recording	Not clearly mentioned
Ding et al. (2014)	fMRI	18	Yes	Video-EEG recording	Yes
Li et al. (2015)	fMRI	20	Yes	Video-EEG recording	Yes
van der Kruijs et al. (2014)	fMRI	21	Yes	Video-EEG recording (in some)	Yes
van der Kruijs et al. (2012)	fMRI	13	Yes	Video-EEG recording (in some)	Yes
Li et al. (2015)	fMRI	20	Yes	Video-EEG recording	Not clearly mentioned
Arthuis et al. (2014)	PET	16	Yes	Video-EEG recording	No standard psychiatric assessment
Allendorfer and Szaflarski (2014)	fMRI	Not mentioned (anecdotal report)			

3. Results

3.1. Traditional magnetic resonance imaging (MRI)

Three descriptive studies investigated brain MRI abnormalities in patients with PNES. In one study, markers of brain abnormalities in patients with PNES were studied to explore whether brain disorders were associated with an increased risk of PNES [11]. Evidence of epileptiform EEG changes, MRI abnormalities, and neuropsychological deficits was obtained from the records of 206 patients with pure PNES. At least one marker of brain disorder was detected in 22.3% of the patients (MRI changes in 27% of those examined or 9.7% of the whole group, epileptiform potentials in 8.7%, and neuropsychological deficits in 9.7% of the whole group). The authors concluded that brain diseases play a role in the development of PNES [11]. This study was limited because of the lack of a healthy control group. In another retrospective study, which did not have a healthy control group either, MRI results of 173 patients were reviewed. A total of 39 (22.6%) patients had abnormal MRI findings [12]. In another previous study that suffers from the same limitation as above, 76% of the patients with PNES studied had unilateral cerebral abnormalities on neuroimaging [13].

In summary, despite the frequent observation of brain MRI abnormalities in patients with PNES, no cause-and-effect relationship could be established based on these studies because of significant methodological limitations.

3.2. Advanced magnetic resonance imaging (MRI)

Four small, but well-designed, case–control studies investigated subtle imaging abnormalities (e.g., voxel-based morphometry, cortical thickness analysis, cortical surface area, connectivity characteristics, white matter diffusion abnormalities) in patients with PNES. In a recent study, the authors investigated 20 patients with PNES and 40 healthy subjects matched for age and sex [14]. All subjects underwent two distinct morphologic whole-brain MR measurements, voxel-based morphometry, and cortical thickness analysis, in a multimethod approach. None of the patients had serious medical or neurological illness, substance abuse problems, or psychotic disorder or were taking antipsychotic drugs. Voxel-based morphometry and cortical thickness analyses in patients with PNES revealed abnormal cortical atrophy of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally [14]. A more recent study evaluated cortical thickness, cortical surface area, curvature, and sulcal depth in patients with PNES [15]. FreeSurfer software was used to identify differences between 37 patients with PNES and 37 healthy controls. No difference in cortical surface area and curvature was detected between the groups. Patients with PNES had increased cortical thickness in the left insula and the left and right medial-orbitofrontal and left lateral-orbitofrontal regions; and decreased cortical thickness in the left and right precentral, right enthorinal, and right lateral-occipital regions compared to healthy controls. Sulcal depth was increased at the level of the left and right insula, right rostral anterior cingulate, right posterior cingulate, and left cuneus and reduced at the level of the right and left medial-orbitofrontal sulci in patients with PNES compared to healthy controls [15]. Another recent study tried to assess the connectivity characteristics of the uncinate fasciculus in patients with PNES and matched healthy controls [16]. Eight patients with PNES and eight age- and sex-matched healthy controls underwent 3-T MRI and 32-direction diffusion tensor imaging (DTI). Computation of DTI indices including fractional anisotropy and diffusion tensor tractography was performed. Patients with PNES exhibited a significantly greater number of uncinate fasciculus streamlines in the right hemisphere tract than in the left hemisphere ($p = 0.031$); such difference was not observed in controls ($p = 0.81$). The authors concluded that the observed differences in emotion processing between healthy individuals and patients with PNES may be related to the differences in the rightward asymmetry in the number of uncinate fasciculus streamlines in patients with PNES [16]. Finally, in another study, the authors investigated white matter diffusion abnormalities in patients with PNES [17]. Diffusion tensor imaging data were collected at 3T in 16 patients with PNES and 16 age- and sex-matched healthy controls. Diffusion tensor imaging indices including fractional anisotropy and mean diffusivity were compared between patients with PNES and healthy controls using tract-based spatial statistics. Significantly higher fractional anisotropy values were observed in patients with PNES in the left corona radiata, left internal and external capsules, left superior temporal gyrus, and left uncinate fasciculus. Their findings suggested that patients with PNES have significantly altered white matter structural connectivity when compared to healthy controls. These abnormalities were present in left hemispheric regions associated with emotion regulation and motor pathways [17].

In summary, four recent studies provide evidence for the existence of subtle structural and connectivity brain abnormalities in patients with PNES.

3.3. Functional MRI (fMRI)

Six small, but well-designed, case–control functional imaging studies and one anecdotal report investigated brain abnormalities in patients with PNES. In one study of functional connectivity networks from resting-state fMRI signal correlations and structural connectivity networks from diffusion tensor imaging tractography in 17 patients with PNES and 20 healthy controls [18], it was observed that patients